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PATENTS
Attorney Docket No. ABGX-2 CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION

Applicants	:	Michael Gallo, *et al.*
Application No.	:	09/375,924 Confirmation No. : 5797
Filed	:	August 17, 1999
For	:	Generation of Modified Molecules with Increased Serum Half-Lives
Group Art Unit	:	1644
Examiner	:	Marianne DiBrino, Ph.D.

Palo Alto, CA 94301
June 29, 2004

Mail Stop Amendment
Hon. Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE UNDER 37 C.F.R. § 1.111

Sir:

In response to the Supplemental Office Action mailed **March 9, 2004**, applicants petition concurrently herewith for a one (1) month extension of time, extending time to respond to and including **July 9, 2004**, and submit the following remarks.

Applicants thank the Examiner for issuing the Supplemental Office Action to identify with clarity the reference cited in the previous Office Action.

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Applicants also enclose herewith a copy of Waldman and Strober, "Metabolism of immunoglobulins," P. Kallos and B. H. Waksman, Eds., *Progress in Allergy* 13:1-110, S. Karger, Basel, NY, 1969, as requested by the Examiner.

The Examiner's First Set of Rejections under 35 U.S.C. § 103(a) Is in Error and Should Be Withdrawn.

The Examiner has rejected claims 52-61 under 35 U.S.C. § 103(a) as having been obvious over WO 96/18412 to Strom *et al.* (Strom) in view of Scand. J. Immunol. 40, 457-65, 1994 to Kim *et al.* (Kim I), Eur. J. Immunol. 1994, 24: 2429-34 to Kim *et al.* (Kim II), and known facts said to be disclosed in the instant specification. For the reasons advanced below, applicants respectfully submit that the rejections are in error and should be withdrawn.

Prima Facie Case

There are three requirements to establish a *prima facie* case of obviousness. First, the prior art references must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Second, there must be some suggestion or motivation contained in the cited references, or in the knowledge generally available to the skilled artisan, to combine reference teachings to reach the claimed invention. Third, the prior art must provide a reasonable expectation that the suggested combination will be successful. The Examiner has the initial burden of factually supporting any *prima facie* conclusion of obviousness. *See* M.P.E.P. § 2142.

The Examiner has failed to make the necessary showings. The Examiner's obviousness rejections are therefore in error and should be withdrawn.

Teaching All Claim Limitations

The Examiner has failed to show that the cited references teach or suggest all the claim limitations. The Examiner states:

> It would have been prima facie obvious ... to have extended the serum half life of an antibody by making an antibody comprising the protein taught by [Strom] and further comprising an Fc IgG region capable of binding FcRb in a pH dependent manner as taught by [Kim I] and [Kim II].[1]

None of the cited references disclose the explicit claim limitation that the antibody whose half-life is to be extended is already capable of binding FcRn. To the extent that the Examiner reads Strom to disclose this limitation, applicants respectfully submit that the Examiner's reading of Strom is in error.

Strom teaches the modification (to confer FcRn-binding capability so as to increase *in vivo* half life) of cytokines that are initially incapable of binding FcRn. More particularly, Strom teaches that the "cytokine" to be modified "can be an interleukin, such as IL-10, IL-6, IL-4, IL-1, IL-2, IL-3, IL-5, IL-7, IL-8, IL-9, IL-12, or IL-15. Other useful cytokines include GM-CSF, G-CSF, interferons (e.g., IFN-α, IFN-β, and IFN-γ), and tumor necrosis factors (e.g., TNF-α and TNF-β)."[2] Strom also teaches that "[b]y 'cytokine' is meant any of the *non-antibody* proteins released by one cell population (e.g., primed T-lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an

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[1] March 9, 2004 Supplemental Office Action, paragraph 4, as continued on page 3.

[2] Strom, page 9, lines 21-26.

immune response."[3] Thus, Strom not only fails to teach extending the serum half-life of an antibody that already binds FcRn, but it in fact explicitly teaches away from this claim limitation.

Furthermore, neither Kim I nor Kim II teach the modification of an antibody that already binds FcRn to extend its serum half life. Kim I and Kim II teach that serum persistence and enhanced binding to FcRn require the presence of two "functional catabolic sites" in murine IgG1 molecules and IgG1 fragments.[4] Kim I also teaches that "[t]agging of a protein with an Fc-derived fragment containing one functional catabolic site would be predicted to be ineffective" in extending the protein's serum half life.[5]

Together, the Kim I and Kim II references teach that a dimer of two Fc-derived peptide fragments, each containing a functional catabolic site, is necessary for FcRn binding.[6] They teach that a heterodimer, consisting of one Fc-derived fragment containing a functional catabolic site and one Fc-derived fragment containing a non-functional catabolic site, is ineffective in binding FcRn and increasing serum persistence.[7] If a protein, such as an antibody, already comprises a dimer containing two functional catabolic sites, however, nothing in Kim I

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[3] Strom, page 10, lines 11-15 (emphasis added).

[4] Kim I, page 463-64; Kim II, page 2433.

[5] Kim I, page 464.

[6] Kim I, page 463-64; Kim II, page 2433.

[7] Kim I, page 463-64; Kim II, page 2433.

or Kim II teaches that the serum half life of such a protein could be extended by fusing an additional functional catabolic site to the end of each of the two fragments in the dimer.

Thus, none of Strom, Kim I, or Kim II teaches an explicit limitation of the instant claims, namely, that the antibody whose half life is to be extended is already capable of binding FcRn, *i.e.*, already comprises a dimer containing two functional catabolic sites. Because none of the cited references teaches an explicit claim limitation, the combination of the cited references could not have resulted in the claimed invention. Thus, having failed to make the necessary factual showing for a *prima facie* case of obviousness, the Examiner's rejections are in error and should be withdrawn.

Motivation to Combine

Even assuming *arguendo* that the cited references teach all of the limitations of the claimed invention, the Examiner has failed to make an adequate showing of motivation to combine.

The Examiner's factual burden includes findings of objective evidence of a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002); *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000); *In re Rouffet*, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) ("To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court *requires* the examiner to show a motivation to combine the references that create the case of obviousness.") (emphasis added).

"The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. The need for specificity pervades this authority." *In re Lee*, 61 USPQ2d at 1433 (internal quotations and citations omitted). "[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Absent such thorough, searching, objective, specific and particularized findings, there can be no *prima facie* case, *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002); absent a *prima facie* case, an applicant is entitled, without more, to his patent, *In re Glaug*, 62 USPQ2d 1151 (Fed. Cir. 2002).

By way of satisfying the burden of identifying a motivation to combine, the Examiner states:

> One of ordinary skill in the art ... would have been motivated to [combine the cited references] in order to produce a protein with increased serum persistence and avidity of binding to FcRb as taught by [Strom, Kim I, and Kim II], and because [Kim I] and [Kim II] teach the need for two FcRn binding sites to significantly increase half life.[8]

Although the Examiner proffers the conclusion that a skilled artisan would have been motivated to "produce a protein with increased serum persistence and avidity of binding to FcRb," the Examiner has failed to show a specific motivation to combine the cited references.

[8] March 9, 2004 Supplemental Office Action, paragraph 4, as continued on page 3.

The cited references, in fact, teach away and would not have motivated a skilled artisan to specifically combine the cited references to produce the claimed invention.

Strom teaches the modification (to confer FcRn-binding capability so as to increase *in vivo* half life) of cytokines that are initially incapable of binding FcRn. More particularly, Strom teaches that the "cytokine" to be modified "can be an interleukin, such as IL-10, IL-6, IL-4, IL-1, IL-2, IL-3, IL-5, IL-7, IL-8, IL-9, IL-12, or IL-15. Other useful cytokines include GM-CSF, G-CSF, interferons (e.g., IFN-α, IFN-β, and IFN-γ), and tumor necrosis factors (e.g., TNF-α and TNF-β)."[9] Strom also teaches that "[b]y 'cytokine' is meant any of the *non-antibody* proteins released by one cell population (e.g., primed T-lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response."[10] Thus, not only does Strom not teach extending the serum half-life of an antibody, or any other protein that already binds FcRn, but it in fact teaches away from the claimed invention. Strom provides no motivation to combine its teachings with the teachings of Kim I and Kim II to produce the claimed invention.

Furthermore, neither Kim I nor Kim II teach the modification of an antibody or any other protein that already binds FcRn to extend its serum half life. Kim I and Kim II teach that serum persistence and enhanced binding to FcRn require the presence of two "functional

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[9] Strom, page 9, lines 21-26.

[10] Strom, page 10, lines 11-15 (emphasis added).

catabolic sites" in murine IgG1 molecules and IgG1 fragments.[11] Kim I also teaches that "[t]agging of a protein with an Fc-derived fragment containing one functional catabolic site would be predicted to be ineffective" in extending the protein's serum half life.[12]

Together, the Kim I and Kim II references teach that FcRn binding requires a dimer of two Fc-derived peptide fragments, each containing a functional catabolic site.[13] They teach that a heterodimer, consisting of one Fc-derived fragment containing a functional catabolic site and one Fc-derived fragment containing a non-functional catabolic site, is ineffective in binding FcRn and increasing serum persistence.[14] If a protein, such as an antibody, already comprises a dimer containing two functional catabolic sites, however, there is nothing in Kim I or Kim II that suggests to one skilled in the art that the serum half life of such a protein could be extended by fusing an additional functional catabolic site to the end of each of the two fragments in the dimer. Thus, Kim I and Kim II provide no motivation to combine their teachings with the teachings of Strom to produce the instant invention.

Since the Examiner has not shown that a suggestion to combine the reference teachings existed either in the cited references or in the knowledge generally available in the art

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[11] Kim I, page 463-64; Kim II, page 2433.

[12] Kim I, page 464.

[13] Kim I, page 463-64; Kim II, page 2433.

[14] Kim I, page 463-64; Kim II, page 2433.

at the time of invention, the Examiner has failed to make the necessary factual showing for a *prima facie* case of obviousness. Thus, the rejections are in error and should be withdrawn.

Reasonable Expectation of Success

Even assuming *arguendo* (i) that the cited references teach all of the claim limitations and (ii) that one would have been motivated to combine the cited references to produce the claimed invention, the Examiner has failed to show that there existed in the prior art a reasonable expectation of success in so combining the cited references. The Examiner does not proffer any evidence of a reasonable expectation of success, either in the cited references or in the prior art, to support a *prima facie* case of obviousness. Having failed to make the necessary factual showing, the Examiner's rejections are in error and should be withdrawn.

Secondary Indicia of Nonobviousness

For the reasons stated above, the Examiner has failed to establish a *prima facie* case of obviousness. Even assuming *arguendo* that a *prima facie* case of obviousness has been established, however, the final determination of obviousness must be proved by a preponderance of all the evidence. This includes both the evidence already set forth by applicants in opposition to the alleged *prima facie* case, *supra* pp. 2-9, and any additional arguments and evidence of secondary considerations. M.P.E.P. § 2142. Such secondary considerations may include the skepticism of experts. M.P.E.P. § 2141.

In August 1998, the applicants applied to the National Cancer Institute for a grant to fund research related to the claimed invention. In December 1998, the applicants received a letter enclosing a "Summary Statement" from the initial review group. The Summary Statement, attached herein as Exhibit I, included critiques by experts in the art discussing the merits of the applicants' proposed approach. In the second critique, the expert in the art stated, "[w]hether the approach proposed in this application is likely to succeed is the question. The modification of an IgG molecule to contain an additional FcRp binding region presents a number of problems."[15] The applicants were required to resubmit the funding application with additional arguments and explanations before the grant was allowed.

This probative evidence of skepticism stands in contrast to the Examiner's unsupported hindsight assumption that there would have been a reasonable expectation of success. Thus, applicants respectfully submit that the Examiner's rejections are in error and should be withdrawn.

The Examiner's Second Set of Rejections under 35 U.S.C. § 103(a) Is in Error and Should Be Withdrawn.

The Examiner has rejected claims 52-61 under 35 U.S.C. § 103(a) as having been obvious over WO 96/18412 to Strom *et al.* (Strom) in view of Scand. J. Immunol. 40, 457-65, 1994 to Kim *et al.* (Kim I), Eur. J. Immunol. 1994, 24: 2429-34 to Kim *et al.* (Kim II), WO 97/34631 to Ward (Ward) and known facts said to be disclosed in the instant specification.

[15] Exhibit I, pages 2-3.

For the reasons advanced below, applicants respectfully submit that the rejections are in error and should be withdrawn.

Prima Facie Case

There are three requirements to establish a *prima facie* case of obviousness. First, the prior art references must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Second, there must be some suggestion or motivation contained in the cited references, or in the knowledge generally available to the skilled artisan, to combine reference teachings to reach the claimed invention. Third, the prior art must provide a reasonable expectation that the suggested combination will be successful. The Examiner has the initial burden of factually supporting any *prima facie* conclusion of obviousness. *See* M.P.E.P. § 2142.

The Examiner has failed to make the necessary showings. The Examiner's obviousness rejections are therefore in error and should be withdrawn.

Motivation to Combine

The Examiner has failed to make an adequate showing of motivation to combine.

The Examiner's factual burden includes findings of objective evidence of a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002); *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000); *In re Rouffet*, 47 USPQ2d 1453, 1457–58 (Fed. Cir. 1998) ("To prevent the use of hindsight based on the

invention to defeat patentability of the invention, this court *requires* the examiner to show a motivation to combine the references that create the case of obviousness.") (emphasis added).

"The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. The need for specificity pervades this authority." *In re Lee*, 61 USPQ2d at 1433 (internal quotations and citations omitted). "[P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

Absent such thorough, searching, objective, specific and particularized findings, there can be no *prima facie* case, *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002); absent a *prima facie* case, an applicant is entitled, without more, to his patent, *In re Glaug*, 62 USPQ2d 1151 (Fed. Cir. 2002).

By way of satisfying the burden of identifying a motivation to combine, the Examiner states:

> One of ordinary skill in the art ... would have been motivated to [combine the cited references] in order to produce a protein with increased serum persistence and avidity of binding to FcRb as taught by [Strom, Kim I, and Kim II], and because [Kim I] and [Kim II] teach the need for two FcRn binding sites to significantly increase half life and because [Ward] teaches that Ig constant domains may be expressed with an Fc domain or an entire

Fc-hinge domain to produce a recombinant protein with enhanced biological stability.[16]

Although the Examiner proffers the conclusion that a skilled artisan would have been motivated to "produce a protein with increased serum persistence and avidity of binding to FcRb," the Examiner has failed to show a specific motivation to combine the cited references. The cited references, in fact, teach away and would not have motivated a skilled artisan to specifically combine the cited references to produce the claimed invention.

The Examiner asserts that Ward "teaches that Ig constant domains may be expressed with an Fc domain or an entire Fc-hinge domain to produce a recombinant protein with enhanced biological stability." Applicants respectfully submit that the Examiner's reading of Ward is in error. References must be considered as a whole; portions that teach away from the claimed invention may not be disregarded. *Bausch & Lomb, Inc.* v. *Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416, 419 (Fed. Cir. 1986); *Panduit Corp.* v. *Dennison Manufacturing Co.*, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987); *In re Wesslau*, 147 USPQ 391, 393 (C.C.P.A. 1965). A complete reading of the Ward disclosure makes clear that, to extend the serum half-life of an antibody or protein that already is capable of binding FcRn, Ward teaches mutating the protein directly at critical residues in the already existing FcRn binding sites and screening for mutants with extended serum half lives. Because of this, Ward does not teach or suggest a motivation to combine the cited references and in fact teaches away from the claimed invention.

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[16] March 9, 2004 Supplemental Office Action, paragraph 5, as continued on page 5.

To illustrate, Ward teaches that its invention concerns "mutants in which one or more of the *natural* residues at the CH2-CH3 domain interface of the Fc-hinge fragment have been exchanged for alternate amino acids."[17] Ward also teaches that "[t]o generate a domain, antibody or antibody construct with a longer half-life, one would modify the *natural* residues at the CH2-CH3 domain interface of the Fc-hinge with either form the 'catabolic control site' or are in close proximity to it."[18] Ward also teaches that "to simply modify a given antibody at one or more of the residues disclosed herein either at, or in proximity to, the catabolic control site" is "particularly suited to producing antibodies with increased serum half-lives."[19] Finally, Ward also teaches that "[a]n antibody or recombinant protein that was found to be cleared from the body more quickly than ideally desired could be engineered at the residues identified herein, or in the vicinity of amino acids that are discovered to directly interact with FcRn, such that its *in vivo* half life was increased."[20] Thus, it is clear that Ward contemplates direct modification to increase the effectiveness of the naturally occurring FcRn-binding domains for proteins such as antibodies in which such domains are already present.

In contrast, Ward teaches fusing FcRn-binding protein fragments to confer serum persistence on proteins that do not already have FcRn-binding capability. Moreover, Ward teaches not only fusions with wild-type FcRn-binding protein fragments, but also more

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[17] Ward, page 4, lines 12-14 (emphasis added).

[18] Ward, page 6, lines 17-19 (emphasis added).

[19] Ward, page 15, lines 7-9.

[20] Ward, page 6, lines 5-8.

particularly fusions with protein fragments modified at the natural residues involved in FcRn binding, as described above, so that the chimeric proteins produced by the fusion will have an extended serum half-life as compared to a fusion with a wild-type FcRn-binding protein fragment. Although the Ward disclosure occasionally refers to the use of this fusion method with "any protein," a close reading of the text of the Ward disclosure as a whole shows that the method was not intended to be applicable for extending the serum half-life of proteins already capable of binding FcRn.[21]

To illustrate, Ward teaches that "Fc or Fc-hinge domains may be linked to any protein to produce a recombinant fusion with enhanced biological stability, or certain mutants may be employed to create antibodies or fusion proteins with increased half lives."[22] Here, the discussion of the fusion method and the mutation method in the alternative implies that the fusion method was not contemplated to apply to antibodies. Ward also teaches that "for example, interleukin-2, interleukin-4, γ-interferon, insulin, T cell epitopes and the like, and even TCR V_α V_β" are all examples of proteins whose stability could be increased via the fusion

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[21] Notwithstanding the inclusion of the word "antibodies" in the statement on page 3, lines 13-19 ("disclosed herein are methods of making an agent with altered serum half-life by conjugating or otherwise binding of that agent to a moiety identified as having an increased serum half-life through its interaction with FcRn. Such agents would include, but are not limited to antibodies, fragments of antibodies, hormones, receptor ligands, immunotoxins, therapeutic drugs of any kind, T-cell receptor binding antigens and any other agent that may be bound to the increased serum half life moieties of the present invention"), reading Ward as a whole clearly shows that the fusion method is meant to apply only to non-FcRn binding "agents." Indeed, the very next paragraph teaches the mutation method as being appropriate for an "FcRn binding protein or peptide." Ward, page 3, lines 20-21.

[22] Ward, page 8, lines 10-12.

method.[23] Antibodies are not mentioned, and none of these proteins are already capable of binding FcRn.

This reading of Ward is confirmed by the Ward claims. The Examiner cites claims 4, 8, 12, 13, and 14 in support of the proposition that Ward teaches the combination of Ig constant domains with Fc or Fc-hinge domains. Applicants submit that the Examiner's reading of the claims is incorrect. The cited claims merely teach the fusion method for proteins that are not already capable of binding FcRn; they do not teach the fusion method for an antibody.

That claim 13 is directed to "antigen binding polypeptide" is of no moment as it refers to an antibody variable domain, not a constant domain. In contrast, claims 16-21 explicitly claim the mutation method for increasing the stability of an antibody. This is paralleled in the specification on pages 14-15, in which Ward first teaches "coupling a protein or an *antibody variable domain* to an increased half life mutant domain,"[24] and then, in the following paragraph, teaches that "[a]nother method ... is to simply modify a given antibody at one or more residues disclosed herein."[25]

Thus, Ward in its entirety teaches the use of one method (the linking of an Fc or Fc-hinge domain) for enhancing the stability of proteins not already capable of binding FcRn,

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[23] Ward, page 10, lines 20-22; see also page 14, lines 17-18.

[24] Ward, page 14, line 28 to page 15, line 1 (emphasis added).

[25] Ward, page 15, lines 7-9.

and another method (direct mutation of the critical residues involved in FcRn binding) for enhancing the stability of proteins already capable of binding FcRn. Taken as a whole, Ward does not teach the expression of an Ig constant domain linked to an Fc or Fc-hinge domain to enhance its stability. For these reasons, Ward does not provide a motivation to combine its teachings with those of Strom, Kim I, and Kim II to produce the claimed invention.

Strom teaches the modification (to confer FcRn-binding capability so as to increase *in vivo* half life) of cytokines that are initially incapable of binding FcRn. More particularly, Strom teaches that the "cytokine" to be modified "can be an interleukin, such as IL-10, IL-6, IL-4, IL-1, IL-2, IL-3, IL-5, IL-7, IL-8, IL-9, IL-12, or IL-15. Other useful cytokines include GM-CSF, G-CSF, interferons (e.g., IFN-α, IFN-β, and IFN-γ), and tumor necrosis factors (e.g., TNF-α and TNF-β)."[26] Strom also teaches that "[b]y 'cytokine' is meant any of the *non-antibody* proteins released by one cell population (e.g., primed T-lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response."[27] Thus, not only does Strom not teach extending the serum half-life of an antibody or any other protein that already binds FcRn, but it in fact teaches away from the claimed invention. Strom provides no motivation to combine its teachings with the teachings of Kim I and Kim II to produce the claimed invention.

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[26] Strom, page 9, lines 21-26.

[27] Strom, page 10, lines 11-15 (emphasis added).

Furthermore, neither Kim I nor Kim II teach the modification of an antibody or any other protein that already binds FcRn to extend its serum half life. Kim I and Kim II teach that serum persistence and enhanced binding to FcRn require the presence of two "functional catabolic sites" in murine IgG1 molecules and IgG1 fragments.[28] Kim I also teaches that "[t]agging of a protein with an Fc-derived fragment containing one functional catabolic site would be predicted to be ineffective" in extending the protein's serum half life.[29]

Together, the Kim I and Kim II references teach that FcRn binding requires a dimer of two Fc-derived peptide fragments, each containing a functional catabolic site.[30] They teach that a heterodimer, consisting of one Fc-derived fragment containing a functional catabolic site and one Fc-derived fragment containing a non-functional catabolic site, is ineffective in binding FcRn and increasing serum persistence.[31] If a protein, such as an antibody, already comprises a dimer containing two functional catabolic sites, however, there is nothing in Kim I or Kim II that suggests to one skilled in the art that the serum half life of such a protein could be extended by fusing an additional functional catabolic site to the end of each of the two fragments in the dimer. Thus, Kim I and Kim II provide no motivation to combine their teachings with the teachings of Strom to produce the instant invention.

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[28] Kim I, page 463-64; Kim II, page 2433.

[29] Kim I, page 464.

[30] Kim I, page 463-64; Kim II, page 2433.

[31] Kim I, page 463-64; Kim II, page 2433.

Since the Examiner has not shown that a suggestion to combine the reference teachings existed either in the cited references or in the knowledge generally available in the art at the time of invention, the Examiner has failed to make the necessary factual showing for a *prima facie* case of obviousness. Thus, the rejections are in error and should be withdrawn.

Reasonable Expectation of Success

Even assuming *arguendo* (i) that the cited references teach all of the claim limitations and (ii) that one would have been motivated to combine the cited references to produce the claimed invention, the Examiner has failed to show that there existed in the prior art a reasonable expectation of success in so combining the cited references. The Examiner does not proffer any evidence of a reasonable expectation of success, either in the cited references or in the prior art, to support a *prima facie* case of obviousness. Having failed to make the necessary factual showing, the Examiner's rejections are in error and should be withdrawn.

Secondary Indicia of Nonobviousness

For the reasons stated above, the Examiner has failed to establish a *prima facie* case of obviousness. Even assuming *arguendo* that a *prima facie* case of obviousness has been established, however, the final determination of obviousness must be proved by a preponderance of all the evidence. This includes both the evidence already set forth by applicants in opposition to the alleged *prima facie* case, *supra* pp. 10-19, and any additional arguments and evidence of secondary considerations. M.P.E.P. § 2142. Such secondary considerations may include the skepticism of experts. M.P.E.P. § 2141.

In August 1998, the applicants applied to the National Cancer Institute for a grant to fund research related to the claimed invention. In December 1998, the applicants received a letter enclosing a "Summary Statement" from the initial review group. The Summary Statement, attached herein as Exhibit I, included critiques by experts in the art discussing the merits of the applicants' proposed approach. In the second critique, the expert in the art stated, "[w]hether the approach proposed in this application is likely to succeed is the question. The modification of an IgG molecule to contain an additional FcRp binding region presents a number of problems."[32] The applicants were required to resubmit the funding application with additional arguments and explanations before the grant was allowed.

This probative evidence of skepticism stands in contrast to the Examiner's unsupported hindsight assumption that there would have been a reasonable expectation of success. Thus, applicants respectfully submit that the Examiner's rejections are in error and should be withdrawn.

[32] Exhibit I, pages 2-3.

Respectfully submitted,

29 JUNE 2004

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Attachment: Exhibit I (NCI Grant Reviewer's Comments)